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Benzo[d][1,3]dioxole and 3,4-Dichlorophenoxy containing Prop-2-ene-1-one Compound Demonstrated Profoundly High Anti-oxidant Activity

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***Abstract*—**Free radicals such as peroxy radical (ROO·), superoxide anion radical (O_2·-), nitric oxide radical (NO·), hydroxyl radical (HO·), alkoxy radical (RO·), nitrogen species (RNS·), and alkyl radical (R·) are the greatest threat to human survival in modern times. The administration of high doses of anti-oxidants is the best and safest approach towards the management of these complications by their potential in scavenging the circulating free-radicals in the human body. Inspiring from the radical scavenging radical effect of chalcones and also from the commercially available synthetically produced anti-oxidants, the current research was designed where a benzylideneacetophenone scaffold was rationally developed through Claisen-Schmidt reaction and screened for their possible anti-oxidant activity by employing the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay. The tested compound presented an IC_{50} value of 6.72 µM. However, the compound represented a low free-radical scavenging in comparison with the standard drug ascorbic acid which had IC_{50} value of 4.41 µM. The reason for the enhanced anti-oxidant activity may be due to the presence of three non-polar aromatic rings. The research results indicated a higher potency of the chalcone as displayed from the IC_{50} value which will motivate the global research towards the rational development of synthetic low-molecular-weight anti-oxidant molecules and pharmaceutical product development with a perspective of chemoprevention and also offer protection from several neurological diseases.

Keywords*—Chalcone, benzo[d][1,3]dioxole, 3,4-dichlorophenoxy, anti-oxidant, free-radical, scavenging*

INTRODUCTION

Free radicals such as peroxy radical (ROO·), superoxide anion radical (O_2·-), nitric oxide radical (NO·), hydroxyl radical (HO·), alkoxy radical (RO·), nitrogen species (RNS·), and alkyl radical (R·) are the greatest threat to human survival in modern times [1]. Recently, scientists have concluded that behind the pathogenesis of nearly every deadly disease such as Alzheimer's disease, cardiac complications, cancer, nephritic disease, metabolic syndromes, etc., the generation of free radicals and their translated effects remained an utmost cause [2]. In general, it was estimated and reported in the literature that nearly 20,000 free-radicals are generated every day which selectively damage the deoxyribosyl backbone of human DNA, promotes lipid peroxidation, and facilitates oxidation of the polydesaturated fatty acids [3]. Unhealthy lifestyle, food practices, excessive alcohol consumption, cigarette smoking, prolonged exposure to the environmental contaminants, etc. escalates the degree of damage to several folds [4].

The administration of high doses of anti-oxidants is the best and safest approach towards the management of these complications by their potential in scavenging the circulating free-radicals in the human body [5]. Natural components, fruits, foods, and nutraceuticals are the richest source of anti-oxidants. Natural products like flavan-3-ols, anthocyanidins, aurones, flavonols, chalcones, flavanones, proanthocyanidins, flavones, and isoflavones have a very high reputation as free-radical scavengers and are known to possess cytoprotective effect [6].

Inspiring from the radical scavenging radical effect of chalcones and also from the commercially available synthetically produced anti-oxidants, the current research was designed where a benzylideneacetophenone scaffold was rationally developed through Claisen-Schmidt reaction and screened for their possible anti-oxidant activity by employing the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay.

MATERIALS AND METHODS

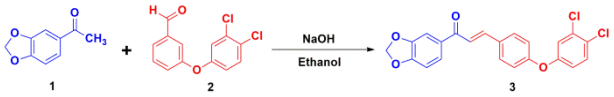
Chemicals and Instrumentation

The starting material and reactant were procured from Sigma Aldrich, Germany through a local dealer. Pre-coated Merck® Silica gel-G TLC plates were utilized to monitor the chemical reaction progress. Double-beam Ultraviolet-Visible Spectrophotometer (Shimadzu® UV-1800) was used for the anti-oxidant characterization. The compound was wholly characterized by spectroscopic techniques such as Fourier-transformed Infrared Spectroscopy (Shimadzu® IR-Affinity-1 instrument), ^{1}H (proton)-NMR Spectroscopy (Bruker® Avance-II), and Mass Spectroscopy (MICROMASS Q-TOF). Elemental

Analysis (PerkinElmer 2400) was employed to determine the ratio of the CHN elements.

Synthesis of target compounds

The chalcone scaffold was fabricated by utilizing the Claisen-Schmidt reaction. The starting substrate 1-(benzo[d][1,3]dioxol-5-yl)ethanone **(1)** containing the acetophenone portion reacts with the reactant 3-(3,4-dichlorophenoxy)benzaldehyde **(2)** having benzaldehyde component to form a β-hydroxyketone function **(3)** in the presence of ethanolic basic solution via aldol condensation mechanism (**Scheme 1**) [7].



Scheme 1. Synthesis of benzo[d][1,3]dioxole and 3,4-dichlorophenoxy containing prop-2-ene-1-one compound.

Synthetic protocol for (*E*)-1-(benzo[d][1,3]dioxol-5-yl)-3-(4-(3,4-dichlorophenoxy)phenyl)prop-2-en-1-one

Equal strength (0.01 M) of substrate **(1)** and reactant **(2)** were made to reflux in the presence of 20 mL sodium hydroxide solution and 25 mL ethanolic solution (90% alcohol). The reaction mixture was made to stand overnight and on a consecutive day, the content was poured over crushed ice containing dilute HCl with vigorous stirring. The chalcone product **(3)** was separated suitably, washed thoroughly with the cold water, and recrystallized [8].

68% yield; FTIR (KBr) υ (cm^{-1}): 3130 (C-H, aromatic), 1728 (C=O), 1661 (C=C, alkene), 1580 (C=C, aromatic), 1474 (-CH_2), 1189 (C-O), 770 (C-Cl); ^{1}H NMR (δ, ppm, $CDCl_3$): 8.15 (6, 1H), 6.9-8.1 (Aromatic, 9H), 6.11 (1, 2H). MS: M^+ 412. Anal. Calcd. for $C_{22}H_{14}Cl_2O_4$: C, 63.94; H, 3.41; N, 0.00. Found: C, 63.17; H, 3.02; N, 0.00.

Anti-oxidant screening

The potential of the tested molecule in absolute scavenging of the DPPH radical was thoroughly explored according to the standard protocol, where 100 µg/mL of the tested compound was added to the 0.1 µM methanolic DPPH solution at an equivalent concentration. After incubating the above mixture at room temperature for exactly half an hour, the absorbance was recorded spectrophotometrically at 517 nm wavelength. Ascorbic acid was considered as the positive control. The IC_{50} value was computed accordingly [9].

RESULTS AND DISCUSSION

Chemistry

The formation of the compound was ascertained by the spectroscopic analysis. The FT-IR spectra stated the formation of chalcone scaffold from two pieces of evidence; first, the appearance of ketonic carbonyl moiety at 1743 cm^{-1}, which easily differentiated the carbonyl function from aldehydes. The second evidence involves the peak representing the alkene (C=C) portion at 1661 cm^{-1}. The formation of chalcone scaffold was also confirmed by the proton-NMR spectra which illustrated the peak 8.15 ppm (HC=CH, alkene). The benzo[d][1,3]dioxole constituent in the ring-A was corroborated from the –CH_2 part in the structure which appeared at 1474 cm^{-1} as well as C-O portion which was predominantly seen at 1189 cm^{-1}. Additionally, the ^{1}H-NMR spectra depicted peak at 6.11 ppm which showed the –CH_2 part in the structure. The 3,4-dichlorophenoxy component in the ring-B was substantiated from the C-Cl peak at 770 cm^{-1}. The aromatic rings in the scaffold were moreover authenticated from the aromatic C=C stretching and C-H aromatic stretching at 1580 cm^{-1} and 3130 cm^{-1}, respectively. Furthermore, the peaks located in the range 6.9-8.1 ppm of the proton-NMR spectra verified the presence of aromatic elements in the scaffold. The beak peak corresponding to the molecular mass of the compound substantiated the formation of chalcone along with the presence of fragmented peaks (m/z 100-200). The close agreement of the practically calculated values of CHN elements with that of theoretically calculated values agreed completely with the formation of the proposed compound.

Anti-oxidant activity

The complete DPPH radical scavenging activity of the chalcone was based on the capability to reduce the ferric form into ferrous. The tested compound presented an IC_{50} value of 6.72 µM. However, the compound represented a low free-radical scavenging in comparison with the standard drug ascorbic acid which had IC_{50} value of 4.41 µM. The reason for the enhanced anti-oxidant activity may be due to the presence of three non-polar aromatic rings. Just as the flavonoid molecules exert a good anti-oxidant due to the multiple active aromatic rings. It is likewise predicted that three non-polar aromatic rings exert lipophilic characteristics and impart excellent anti-oxidant activity.

Table 1: *Anti-oxidant potential of benzo[d][1,3]dioxole and 3,4-dichlorophenoxy containing prop-2-ene-1-one compound.*

Compounds	IC_{50} value (µM)
3	6.72 ± 0.33**
Ascorbic acid	4.41 ± 0.57**

*n = 3; **p<0.01 with respect to standard drug*

CONCLUSION

The synthesized chalcone presented an excellent anti-oxidant activity than that of the standard compound ascorbic acid. The current study revitalizes the approach of adding multiple dynamic scaffolds for enhancing the biological potency. The research results indicated a higher potency of the chalcone as displayed from the IC_{50} value which will motivate the global research towards the rational development of synthetic low-molecular-weight anti-oxidant molecules and pharmaceutical product development with a perspective of chemoprevention and also offer protection from several neurological diseases.

CONFLICT OF INTEREST

No conflict of interest declared.

REFERENCES

[1] Shivhare RS, Mahapatra DK, Nair RR, Deshmukh SN. Schiff's base derivatives of murrayanine demonstrated enhanced anti-oxidant activity than its parent moiety. Indian J Pharm Edu Res 2016; 50(4): 9-15.

[2] Chhajed SS, Upasani CD, Wadher SJ, Mahapatra DK. Medicinal Chemistry. Nashik: Career Publications Private Limited, 2017.

[3] Kamble MA, Mahapatra DK, Dhabarde DM, Ingole AR. Pharmacognostic and pharmacological studies of Bombax ceiba thorn extract. J Pharm Pharmacog Res 2017; 5(1): 40-54.

[4] Mahapatra DK, Bharti SK. Handbook of Research on Medicinal Chemistry: Innovations and Methodologies. New Jersey: Apple Academic Press, 2017.

[5] Mahapatra DK, Bharti SK. Drug Design. New Delhi: Tara Publications Private Limited, 2016.

[6] Mahapatra DK, Bharti SK, Asati V. Anti-cancer Chalcones: Structural and molecular targets perspectives. Eur J Med Chem 2015; 98: 69-114.

[7] Mahapatra DK, Shivhare RS. Anti-microbial Perspective of a Chalcone, (E)-1-(1-methoxy-9H-carbazol-3-yl)-3-(4-(methylsulfonyl)phenyl)prop-2-en-1-one: Fabrication of a Hybrid by Unification of a Natural Product with a Synthetic Component. Int J Agri Life Sci 2018; 4(2): 236-240.

[8] Mahapatra DK, Shivhare RS. 3′,4′-Methylenedioxy Moiety Containing Murrayanine Based Chalcone as Emerging Anti-inflammatory Agent. J Mod Chem Chem Technol 2018; 9(1): 12-16.

[9] Mahapatra DK, Shivhare RS. Synthesizing an anti-oxidant principle 2-(((1-methoxy-9H-carbazol-3-yl)methylene)amino)isoindoline-1,3-dione from N-aminophthalimide and murrayanine. Inventi Med Chem 2017; 2017(4): 1-3.

